REMARKS

By the present Amendment, claims 1, 2 and 4-7 have been amended in response to the Office Action dated March 26, 2001. Claim 3 has been cancelled. Claims 8-19 have been added. Attached hereto is a marked-up version of the changes made to the claims by the present Amendment. The attachment is captioned: **Version with Markings to Show Changes Made**. Claims 1, 2 and 4-19 remain in the application. No new matter has been added by this Amendment. A substitute specification correcting certain typographical errors is also included.

Applicant respectfully requests reconsideration of the claims in view of the foregoing amendment and following remarks.

Rejection Under 35 U.S.C. §112

Claims 1-7 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. This rejection is respectfully traversed.

By the present amendment, claim 3 has been cancelled and claims 1, 2 and 4-7 have been amended. The nomenclature using a double dash has been corrected in each claim and in the specification. Punctuation, such as extra periods and lack of commas, has also been corrected in all claims.

Claim 1 has been amended to clarify that the percentages recited in the claims are intended for a total of the combination of possible compounds. Claim 1 has also been amended through combination with claim 3 in response to the Examiner's objection to use of the phrase "as well as the remainder of conventional injections." The amendments to Claim 1 also clarify claims 2 and 4-6, as those claims are dependent on claim 1.

In response to the Examiner's comment that the phrase "proportion described above" in Claim 7 is improper inferential language, please note that the Second Preliminary Amendment filed March 18, 2002 removed that phrase from Claim 7.

It is therefore respectfully requested that the rejection of claims 1, 2 and 4-7 under 35 U.S.C. §112, second paragraph, be withdrawn.

Rejection Under 35 U.S.C. §102

Claim 1 has been rejected under 35 U.S.C. § 102(b) as anticipated by a published PCT application with international publication number WO 98/08500. This rejection is respectfully traversed.

PCT application WO 98/08500 discloses hypertonic arginine formulations used in treating hemorrhagic shock. The disclosure focuses on L-arginine by fully discussing the benefits of L-arginine and various formulations in which it has been the ingredient of interest, with all other ingredients meriting no discussion. All of the disclosed methods and claims require L-arginine as an essential component. For instance, WO 98/08500 discloses seven examples, all of which illustrate the effects of various solutions containing L-arginine. Example 5 particularly "shows several hypertonic arginine formulations that will be useful for treatment of trauma and shock" with one formulation including L-arginine, sodium chloride and hetastarch. Furthermore, Claims 1-16 all contain L-arginine. Neither the disclosure nor the claims disclose NaCl and hetastarch in combination with any substance other than L-arginine, as effective in the treatment of hemorrhogic shock. In contrast, claim 1 as amended recites a composition that is free of L-arginine.

Because WO 98/08500 does not disclose a pharmaceutical composition without L-arginine as a component, it is respectfully requested that the rejection of claim 1 under 35 U.S.C. §102(b) as being anticipated by WO 98/08500 be withdrawn.

Rejection Under 35 U.S.C. §103

Claims 1-7 have been rejected under 35 U.S.C. § 103(a) as anticipated by a published PCT application with international publication number WO 98/08500. This rejection is respectfully traversed.

WO 98/08500 remains deficient as a reference, as it does not teach a pharmaceutical composition without L-arginine as recited in amended claims 1, 2, and 4-7. The Examiner ignores the absence of L-arginine in the instant invention in making his suggestions of obviousness. Every formulation disclosed in WO 98/08500 contains L-arginine. WO 98/08500 does not suggest that L-arginine could be eliminated from the formulation without rendering the

formulation ineffective. In fact, eliminating L-arginine would destroy the teachings of WO 98/08500, as it is concerned entirely with using L-arginine in various formulations with other compounds.

In addition to teaching away from the absence of L-arginine from the pharmaceutical composition, WO 98/08500 fails to disclose or suggest all the elements of the dependent claims. For example, WO 98/08500 discloses a 7.5% hypertonic saline solution. WO 98/08500 does not suggest how far the concentration of that solution might be lowered nor does it suggest any alternative specific amounts of NaCl in the formulations it does disclose. WO 98/08500 therefore particularly fails to disclose or suggest a solution having between about 4.0 and 4.2 g NaCl as recited in claim 2. Furthermore, WO 98/08500 fails to disclose or suggest any of the elements in claims 5 and 6 such as dextran, carboxymethyl starch, PVP, gelatin derivatives, condensed glucose, glucose, fructose, lactose, glycerin, xylitol, sodium alginate, N-2-hydroxypropylacrylamide, ethylene epoxide, polypropylene glycol, pectin, or pentahydroxyethyl starch.

It is therefore respectfully requested that the rejection of Claims 1, 2 and 4-7 under 35 U.S.C. § 103(a) as being unpatentable over WO 98/08500 be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, Applicant submits that all of the claims now present are allowable, and withdrawal of the rejections and a Notice of Allowance are courteously solicited.

If any impediment to the allowance of the claims remains after consideration of this amendment, and such impediment could be alleviated during a telephone interview, the Examiner is invited to telephone the undersigned at (214) 969-4657 so that such issues may be resolved as expeditiously as possible.

If any applicable fee or refund has been overlooked, the Commissioner is hereby authorized to charge any fee or credit any refund to the deposit account of Akin, Gump, Strauss, Hauer & Feld, L.L.P., No. 01-0657.

Respectfully Submitted,

Date: June 26, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. **(Twice Amended)** An L-arginine free pharmaceutical composition comprising: [1.5--6.9 % (w/v) of one or more substances selected from]

a first substance comprising sodium chloride in an amount between about 1.5% and 6.9% (w/v);

a second substance comprising at least one of [sodium chloride, sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, sodium acetate and Tris (Hydroxy methyl) aminomethane, and 3 ~ 18 % (w/v) of one or more substances selected from] hydroxyethyl starch, dextran, carboxymethyl starch, polyvinyl [--] pyrrolidone (PVP), gelatin derivatives, condensed glucose, glucose, fructose, lactose, glycerin, xylitol, sodium alginate, N-[-]2-hydroxypropylacrylamide, ethylene epoxide[-], polypropylene glycol, pectin, and pentahydroxyethyl starch[; as well as the remainder of conventional injections, as long as sodium chloride is not less than l. 5 % (w/v), and]**, wherein said third substance is present in an amount between about 3 and l8 % total (w/v); and**

a conventional injection comprising at least one of water, physiological saline, balanced buffers, glucose solution, sodium lactate solution, sodium acetate solution, Tris solution, and glucose and sodium chloride solution, wherein said conventional injection is present in an amount between about 75.1% and 95.5% total (w/v).

[is not more than that of in a 6.9 % (w/v) sodium chloride solution or equivalent]

2. **(Amended)** The pharmaceutical composition of Claim 1, wherein

said first substance comprises sodium chloride in an amount between about 2.5 and about 2.7 g; and

said second substance comprises hydroxyethyl starch in an amount between about 7.0 g and about 8.2 g [the composition contains 4.2±0.2g sodium chloride and 7.6±0.6g hydroxyethylstarch] per 100 mL.

Please cancel claim 3 without disclaimer or prejudice.

4. **(Thrice Amended)** The pharmaceutical composition of Claim 1, wherein **said second substance comprises** hydroxyethyl starch, [contains] **at least l0%** [hydroxyethyl starch]

of which has [with] a molecular weight of **about** 25,000-**[-]**45,000 atomic mass units.

5. **(Twice Amended)** The pharmaceutical composition of Claim 1, wherein said **second substance comprises** gelatin derivatives ha[s]**ving** a molecular weight of **about** 20,000-35,000 atomic mass units, **said gelatin derivatives being** [and are] selected from **at least one of** urea[--], conjugated gelatin, modified liquid gelatin, oxidized polygelatin and degraded gelatin polypeptide.

6. **(Twice Amended)** The pharmaceutical composition of Claim 1, wherein **said second substance comprises at least one of** said dextran ha[s]**ving** a molecular weight of **about** 40,000-[-]230,000 atomic mass units**,**[;] said carboxymethylstarch ha[s]**ving** a molecular weight of **about** 30,000-[-]80,000 atomic mass units, said PVP ha[s]**ving** a molecular weight of **about** 5,000-[-]700,000 atomic mass units, said condensed glucose ha[s]**ving** a molecular weight of **about** 8,000-12,000 atomic mass units, said sodium alginate ha[s]**ving** a molecular weight of **about** 20,000-**[-]**26,000 atomic mass units, said pectin ha[s]**ving** a molecular weight of **about** 20,000-40,000 atomic mass units**,**[;] and said pentahydroxyethyl_starch ha[s]**ving** a molecular weight of about 264,000 atomic mass units.

7. **(Twice Amended)** A method for preparing the pharmaceutical composition of Claim 1, comprising:

dissolving [3--l8g of one or more substances selected from hydroxyethylstarch, dextran, carboxymethylstarch, PVP, gelatin derivatives, condensed glucose, glucose. fructose, lactose, glycerin, xylitol, sodium alginate, N--2--hydroxypropylacrylamide, ethylene epoxide-polypropylene glycol, pectin, and pentahydroxyethylstarch,] **an amount between about 3 g and l8 g of said second substance** in **a** total of 100 ml of [one] **said** injection**;** [or mixture of several injections selected from water, physiological saline, balanced buffers, glucose solution, sodium lactate solution, sodium acetate solution, Tris solution, and glucose and]

adding l.5 g of said first substance; and [sodium chloride

and 0—5.4g of one or more substances selected from sodium chloride. sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, sodium acetate, and Tris,

mixing to dissolution to obtain said pharmaceutical composition.] **mixing said**

conventional injection to dissolve said first, second, and third substances therein.

8. The method for preparing the pharmaceutical composition of Claim 7 further comprising:

adding an amount between 0 and about 5.4 g of said third substance, such that the total sodium ion concentration based on said first and third substances does not exceed an equivalent sodium ion concentration in a 6.9 % (w/v) sodium chloride solution.

9. The pharmaceutical composition of Claim 1 further comprising:

a third substance comprising at least one of sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, sodium acetate and Tris (Hydroxy methyl) aminomethane,

wherein the total sodium ion concentration based on said first and third substances does not exceed an equivalent sodium ion concentration in a 6.9 % (w/v) sodium chloride solution.

10. The pharmaceutical composition of Claim 9, wherein

said first substance comprises sodium chloride in an amount of about 1.5 g;

said second substance comprises hydroxyethyl starch in an amount of about 3 g and dextran in an amount of about 9 g;

said third substance comprises sodium bicarbonate in an amount of about 3.4 g; and

said injection comprises physiological saline.

11. The pharmaceutical composition of Claim 9, wherein

said first substance comprises sodium chloride in an amount of about 2.0 g

said second substance comprises PVP in an amount of about 12 g;

said third substance comprises sodium acetate in an amount of about 4 g; and

said injection comprises a 10% glucose solution.

12. The pharmaceutical composition of Claim 1, wherein

said first substance comprises sodium chloride in an amount of about 2.7 g;

said second substance comprises hydroxyethyl starch in an amount of about 7.6 g; and

said injection comprises water.

13. The pharmaceutical composition of Claim 1, wherein

said first substance comprises sodium chloride in an amount of about 1.5 g;

said second substance comprises sodium alginate in an amount of about 18 g; and

said injection comprises water.

14. The pharmaceutical composition of Claim 1, wherein

said first substance comprises sodium chloride in an amount of about 4.4 g;

said second substance comprises condensed glucose in an amount of about 7 g and N-2-hydroxypropylacrylamide in an amount of about 2 g; and

said injection comprises water.

15. The pharmaceutical composition of Claim 1, wherein

said first substance comprises sodium chloride in an amount of about 4.8 g;

said second substance comprises fructose in an amount of about 5 g and xylitol in an amount of about 4 g; and

said injection comprises water.

16. The pharmaceutical composition of Claim 1, wherein

said first substance comprises sodium chloride in an amount of about 6.0 g;

said second substance comprises glycerin in an amount of about 2 g and lactose in an amount of about 5 g; and

said injection comprises water.

17. The pharmaceutical composition of Claim 1 comprising:

a first substance comprising sodium chloride in an amount between about 1.5% and 5.9%(w/v);

a second substance comprising at least one of hydroxyethyl starch, dextran, carboxymethyl starch, polyvinyl pyrrolidone (PVP), gelatin derivatives, condensed glucose, glucose, fructose, lactose, glycerin, xylitol, sodium alginate, N-2-hydroxypropylacrylamide, ethylene epoxide, polypropylene glycol, pectin, and pentahydroxyethyl starch, wherein said third substance is present in an amount between about 3 and 18 % total (w/v); and

an injection comprising at least one of water, physiological saline, balanced buffers, glucose solution, sodium lactate solution, sodium acetate solution, Tris solution, and glucose and sodium chloride solution, wherein said conventional injection is present in an amount between about 76.1% and 95.5% total (w/v),

18. The pharmaceutical composition of Claim 17 further comprising:

a second substance comprising at least one of sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, sodium acetate and Tris (Hydroxy methyl) aminomethane,

wherein the total sodium ion concentration based on said first and third substances does not exceed an equivalent sodium ion concentration in a 5.9 % (w/v) sodium chloride solution.

19. A pharmaceutical composition consisting essentially of:

a first substance consisting essentially of sodium chloride in an amount not

less than about 1.5% (w/v);

a second substance comprising at least one of sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, sodium acetate and Tris (Hydroxy methyl) aminomethane, wherein said second substance is present in an amount between about 0 and 5.4% (w/v).

a third substance consisting essentially of at least one of hydroxyethyl starch, dextran, carboxymethyl starch, polyvinyl pyrrolidone (PVP), gelatin derivatives, condensed glucose, glucose, fructose, lactose, glycerin, xylitol, sodium alginate, N-2-hydroxypropylacrylamide, ethylene epoxide, polypropylene glycol, pectin, and pentahydroxyethyl starch, wherein said third substance is present in an amount between about 3 and 18 % total (w/v); and

an injection consisting essentially of at least one of water, physiological saline, balanced buffers, glucose solution, sodium lactate solution, sodium acetate solution, Tris solution, and glucose and sodium chloride solution, wherein said conventional injection is present in an amount between about 75.1% and 95.5% total (w/v),

wherein the total sodium ion concentration based on said first and second substances does not exceed an equivalent sodium ion concentration in a 6.9 % (w/v) sodium chloride solution.

~~{Novel Pharmaceutical Compositions for Treating and Saving }~~**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

~~{and the Method for the Preparation thereof}~~ **SPECIFICATION**

accompanying

Application for Grant of U.S. Letters Patent

TITLE: NOVEL PHARMACEUTICAL COMPOSITIONS FOR TREATING AND SAVING AND THE METHOD FOR THE PREPARATION THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to a novel pharmaceutical composition for treating and saving the wounded, and to a method for the preparation thereof.

~~{Nowadays blood}~~**[0002] Blood** transfusion and fluid infusion are ~~{the}~~ important measures to treat and save ~~{the}~~ wounded **persons**, especially ~~{the}~~ **persons suffering from** traumatic shock. Usually, the principle of transfusion is "to infuse ~~{component}~~ **components** the patient is deficient in, to supply how much the patient needs". For example, when the patient **has** mainly lost ~~{his}~~ blood, he should be transfused with blood, even though sometimes the patient needs to be transfused with blood from normal individuals. When the patient **has** mainly lost plasma, plasma or plasma volume expander should be transfused to him~~{; when}~~**. When** the patient **has** mainly lost intercellular fluid, physiological saline should be infused. In fact, the treating and saving measures of formulating physiological solutions

on the basis of normal **body** composition ~~{of body}~~, or transfusing with blood from normal individuals to the patient with evident physiopathological changes is to treat the organism as **a** mechanical device, therefore these measures often have **the** following disadvantages:

~~{(1)}~~**[0003] (1)** Blood transfusion: In general, the volume of blood ~~{transfusion closes}~~ **transfused comes close** to or exceeds the volume of blood lost. If a big amount of blood is required, the blood source will be difficult **to obtain**, the cost ~~{is}~~ **will be** expensive~~{. The}~~**, and its** preparation and storage ~~{need}~~ **require** certain conditions. In addition, before transfusion, some time should be taken for blood typing and cross match tests, and only the substitutes could be used for the individuals with rare blood types. Blood transfusion could result in production of anti-~~{-}~~platelet antibodies and anti-~~{-leucocyte}~~ **leukocyte** antibodies, as well as various hematogenic infectious diseases, for example~~{,}~~ AIDS, hepatitis B, hepatitis C~~{-}~~, etc.

[0004] (2) Albumin infusion: There is a great demand, a great expense ~~{difficult}~~**, difficulty in obtaining a** source, complicated preparation method, and certain requirements for~~{,}~~ the method **of** storage **of albumin**. After albumin infusion, it could effuse through capillaries, and couldn't be reabsorbed into vessel. Therefore interstitial edema will occur, and might result in pulmonary edema, renal failure, and cardiac insufficiency, ~~{by contrast enhance the }~~**thus enhancing the possibility for** mortality. Albumin infusion could result in evident decrease of α_1, α_2, β, γ-globulins and fibrinogen, cause reduction of immunity, and affect function of blood coagulation.

[0005] (3) Infusion of fluorocarbon as plasma substitute: ~~{It}~~ **Such infusion** requires a large amount of the substitute and simultaneous inhalation of

oxygen with high component pressure. ~~{0therwise}~~ **Otherwise** the demand of the organism is not met. The fluorocarbon as plasma substitute should be preserved ~~{in}~~ **at a** low temperature, and its transport is not convenient. For example, thirty minutes before infusion, the patient should be injected with ~~{10}~~ **10** mg of dexamethasone. The frozen injection for infusion should be thawed. Thus, the procedures are complicated. After infusion, ~~{the}~~ observation should be continued for 5 – ~~{10min}~~ **10 min**. The infusion of fluorocarbon as plasma substitute could induce adverse reactions, such as anaphylaxis, hypotension, thrombocytopenia, hepatosplenomegaly, reduction of immunity, and abnormality of fibrinolysis system.

[0006] (4) Infusion of balanced buffers~~{, Its}~~**. The** amount **of balanced buffers** infused should be three times more than the volume of blood lost to maintain the blood pressure. ~~{60–80%}~~ **Sixty to eighty percent (60-80%) of** the solution infused could effuse out of the blood vessel, which results in tissue edema (for example, cerebral edema~~{,}~~ **or** pulmonary edema) and renal insufficiency, ~~{it}~~ **which in turn** could cause ~~{the}~~ difficulty for sequential therapy.

[0007] (5) Infusion of physiological saline. ~~{Its}~~ **The** amount **of physiological saline** infused should also be three times more than the volume of blood lost. Its efficacy is poorer than balanced buffers, and its adverse effects are more significant.

[0008] To solve the problems in blood transfusion and infusion, the skilled in the art had studied anti-~~{-}~~shock therapy with hypertonic sodium chloride solution. For example, ~~{7.5%}~~ **7.5%** (w/v) NaC1 solution **as** suggested by Velasco. ~~{But the}~~ **The** hypertonic NaC1 solution**, however,** has some toxicity to the organism.

[0009] Most investigators have proposed intravenous injection of hypertonic NaC1 solution for anti-~~{-}~~shock therapy, but it usually leads to obvious

complications, such as hypotension, rupture of blood cells induced by extra hypertonic solution, cardiac insufficiency, decreased renal function and disorders of **the** nervous system.

[0010] Thus, it can be ~~{showed}~~ **shown** that there is a demand for novel anti-~~{-}~~shock drugs to reverse the physiopathological condition of shock, in order to obtain time for sequential therapy after the emergency treatment, and to create opportunity ~~{with}~~ **for** improved effect of treating and saving the wounded and patients, and ~~{with increased}~~ **increasing** survival rate.

[0011] An object of the present invention is to provide a pharmaceutical composition with **a** convenient source, **that requires** less dosage, **and that has** rapid and better efficacy, less side effects, wider uses, ~~{and without restriction}~~ **is not restricted** by blood type ~~{as well as without}~~ **and does not require** special storage ~~{condition.~~ **}conditions.**

[0012] Another object of the present invention is to provide ~~{the}~~ **a** method for the preparation of the said pharmaceutical composition.

[0013] The present invention proposes a new concept of liquid therapy for shock, based on three aspects of thinking. The first aspect ~~{in connection with}~~ **relates to** the present unreasonable dosage regimen, **and adopts the** following principle ~~{is adopted}~~: "to infuse what component the patient needs, then to infuse how much the patient needs". Based on the physiopathological status of the patient with shock, there is a prior demand for the compound solution containing hypertonic sodium ion (or **a** combination of various crystals~~{,}~~ or **a** combination of various crystals and various colloids, etc.) to preliminarily improve micro-~~{-}~~circulation, tissue perfusion, and hemodynamics immediately. Then in the light of practical demand the isosmotic solution or proper hypoosmotic solution or whole blood or concentrated red blood cell suspension is administered, in order to

permit the latter infused solution better action when the patient's condition has improved preliminarily by the earlier hypertonic solution, and to remit over-{-}dehydration of some cells caused possibly by the hypertonic solution infused earlier. The second aspect~~{, in connection with}~~ **relates to** the present unreasonable ratio of colloids and crystals in the transfusion for patient with shock **when** prepared on **the** basis of their normal physiological concentrations~~{, in}~~**. In** view of the fact that the property and volume-{-}expanding ability of artificial colloids are different from albumin in blood, it is considered that the transfusion with suitable ratio of colloids and crystals~~{, instead of human normal physiological proportion,}~~ should be administered on basis of the physiopathological status of patients**, rather than the normal physiological proportion**. Thus medicine administration according to indications could reduce the dosage, increase the efficacy, and decrease the complications. The third aspect~~{, in connection with a lot of}~~ **relates to** inadequacy in the present anti-{-}shock experimental studies (such as animal model, reasonable concentration and infusion rate of hyperosmotic solutions), a great number of experimental studies have been conducted, and met with success.

[0014] Based on the above three aspects of thinking ~~{form}~~ **from** the theoretical researches and the clinical experiences~~{.}~~**,** the particular embodiments of the present invention have been completed through ~~{the}~~ animal experiments and ~~{the}~~ clinical practice.

[0015] The present invention is achieved through the following embodiments. A pharmaceutical composition comprising ~~{1.5—6.9%}~~ **1.5-6.9%** (w/v) of one or more substances selected from sodium chloride, sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, sodium acetate and Tris (Hydroxy methyl) aminomethane; and 3-~~{18%}~~ **18%** (w/v) of one or more

substances selected form ~~{hydroxyethylstarch}~~ **hydroxyethyl starch**, dextran, carboxy methylstarch, polyvinyl-pyrrolidone (PVP), gelatin derivatives, condensed glucose, glucose, fructose, lactose, glycerin, xylitol, sodium alginate, N-2-hydroxypropylacrylamide, ethylene epoxide-~~{~~ ~~}~~polypropylene glycol, pectin, mannitol, and penta ~~{hydroxyethylstarch}~~ **hydroxyethyl starch** (Pentastarch) as well as the remainder of conventional injections, as long as sodium chloride is not less than ~~{1. 5%}~~ **1.5%** (w/v), and the concentration of sodium ion is not more than that of ~~{in 6. 9%}~~ **6.9%** (w/v) sodium chloride solution or equivalent.

[0016] The preferred composition of the present invention consisting of 4.2± ~~{0.2g}~~ **0.2 g.** sodium chloride and 7.6± ~~{0.6g hydroxyethylstarch per 100ml.~~ ~~}~~**0.6 g. hydroxyethyl starch per 100 ml.**

[0017] In the composition, the said hydroxyethylstarch contains at least ~~{10%}~~ **10%** hydroxyethylstarch with molecular weight of ~~{25, 000--45, 000.~~ ~~}~~**25,000-45,000 atomic mass units (amu).**

[0018] The said dextran has molecular weight of ~~{40, 000--230, 000, carboxymethylstarch}~~ **40,000-230,000 amu, carboxymethyl starch** has molecular weight of ~~{30, 000--80, 000}~~ **30,000-80,000 amu**, PVP has molecular weight of ~~{5, 000--700, 000}~~ **5,000-700,000 amu**, condensed glucose has molecular weight of ~~{8, 000--12, 000}~~ **8,000-12,000 amu**; sodium alginate has molecular weight of ~~{20, 000--26, 000;}~~ **20,000-26,000 amu,** pectin has molecular weight of ~~{20, --000--40, --000; pentahydroxyethylstarch is}~~ **20,000-40,000 amu, and pentahydroxyethyl starch (**the product of DuPont Company (Pentastarch) ~~{with}~~**) has** molecular weight of ~~{264, 000.~~ ~~}~~**264,000 amu.**

[0019] The said gelatin derivatives have molecular weight of ~~{20, 000--35, 000,}~~ **20,000-35,000 amu** and are selected from urea~~{--}~~, conjugated gelatin,

modified liquid gelatin, oxidized polygelatin and degraded gelatin poly-{-}peptide.

[0020] Conventional injections are selected from water for injection, physiological saline, balanced buffers, glucose solution, sodium lactate solution, sodium acetate solution, Tris solution, ~~{and}~~ glucose **solution** and sodium chloride solution.

[0021] The composition of the present invention is prepared ~~{as}~~ **according to the** following procedure: dissolving 3-~~{18g}~~ **18 g.** of total amount of one or more substances selected from ~~{hydroxyethylstarch, dextran, carboxymethylstarch}~~ **hydroxyethyl starch, dextran, carboxymethyl starch**, PVP, gelatin derivatives, condensed glucose, glucose, fructose, lactose, glycerin, xylitol, sodium alginate, N-~~{-}~~2-~~{-}~~hydroxypropylacrylamide, ethylene epoxide~~{-}~~, polypropylene glycol, pectin, ~~{mannitol, and pentahydroxyethylstarch}~~ **and pentahydroxyethyl starch** in 100 ml of total volume of one injection or mixture of several injections selected from water for injection~~{.}~~, physiological saline, balanced buffers, glucose solution, sodium lactate solution, sodium acetate solution, Tris solution, ~~{and}~~ glucose **solution** and sodium chloride solution; then adding ~~{1. 5g}~~ **1.5 g.** sodium chloride and ~~{0 5.4g}~~ **0-5.4 g.** of one or more substances selected from sodium chloride, sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, sodium acetate, and Tris; with the proportion described above, then mixing, and dissolving, to obtain the composition of the present invention.

[0022] The preferred technical embodiments are as follows: (i) preparation of ~~{hydroxyethylstarch}~~ **hydroxyethyl starch**: According to the proportion of ~~{1:0. 8 0. 875: 0. 04 0. 042}~~ **1:0.8-0.875:0.04-0.042** (w/v/v)~~{,}~~ corn starch or sorghum starch, ~~{and}~~ 95% ethanol, and 35-~~{-}~~38% hydrochloric

acid are mixed, the temperature is raised to 65-{-80} **80℃i** for hydrolysis of starch, {16%} **16%** sodium hydroxide solution is added in proportion of {0. 6--0. 7: 1} **0.6-0.7:1** (v/w) of stated solution versus starch. Then ethylene epoxide is added in proportion of 0. 35-{-}0. 5: {1} **1** (w/w) of ethylene epoxide versus starch, then the mixture is heated to 65-{-}75℃i to cause starch hydroxyethylation. (ii) Formulation of the composition: Appropriate volume of water is added, to prepare {7.6±0.6%(w/v)} **7.6±0.6%(w/v)** hydroxyethylstarch solution. Suitable amount of activated charcoal is added to discolor the solution through adsorption. After filtration, the pH is adjusted to {5. 5-}**5.5**-7, and the total of 4± {0.2g} **0.2 g.** of sodium chloride is added{,}**. A** suitable amount of activated charcoal is added again for adsorption and discolor action. After {filtrated} **filtration** through {0. 8anm} **0.8μm** micro-{-}porous filter, the preferred composition of the present invention is obtained.

[0023] The present invention is further illustrated in detail by the following examples.

Preparative example.

Preparation of {hydroxyethylstarch. }**hydroxyethyl starch.**

{100g Corn}**[0024]** **100 g. corn** or sorghum starch are mixed with {87ml} **87 ml.** of 95% ethanol and {4. 2} **4.2** ml. of 35% hydrochloric acid. The temperature is raised to {704.} **70℃o** to hydrolyze starch then {60ml at 16%} **60 ml. of 16%** sodium hydroxide solution is added, then {45g} **45 g.** epoxyethane is added, and the mixture is heated to {7045} **70e** to complete hydroxyethylation of starch. According to the formula and preparative method described above {hydroxyethylstarch}, **hydroxyethyl starch** with molecular weight of {25, 000--45, 000} **25,000-45,000 amu** is obtained.

[0025] Example 1.

Prepare according to the following proportion:

hydroxyethylstarch	~~{7.6g}~~ **7.6 g.**
sodium chloride	~~{4.2g}~~ **4.2 g.**
water for in injection	added to ~~{100ml}~~ **100 ml.**

~~{7. 6g hydroxyethylstarch}~~**[0026]** **7.6 g. hydroxyethyl starch** are dissolved in ~~{100}~~ **100** ml. of water for injection. ~~{0. 5g}~~ **One half gram (0.5 g.)** of activated charcoal is added, and the mixture is heated at 90℃t for ~~{15}~~ **15** min under stirring. After filtration through **an** asbestos plate filter, ~~{4. 2g}~~ **4.2 g** sodium chloride (purity pharmaceuticals use) are added, and dissolved with stirring. ~~{0.5g}~~ **0.5 g.** activated charcoal is added, and the mixture is heated at 90℃t for ~~{10}~~ **10** min. under stirring. After filtration through **an** asbestos plate filter and ~~{0. 8thm}~~ **0.8μm** micro-porous filter~~{. resulted}~~**, the resultant** filtrate is transferred into ~~{250ml}~~ **250 ml.** or 500-ml. glass or plastic bottles (bags)~~{, after}~~**. After** sealing, the bottles or bags are ~~{1.05}~~ **1.05** kg/cm^2 and ~~{121-123}~~ **121-123** ℃ for ~~{15—30min}~~ **15-30 min.** for sterilization, to obtain the pharmaceutical composition of the present invention.

[0027] Example 2.

Prepare according to the following proportion:

dextran {9g} **9 g.**

{hydroxyethylstarch 3g} **hydroxyethyl starch** **3 g.**

sodium chloride {1.5g} **1.5 g.**

sodium bicarbonate {3.4g} **3.4 g.**

physiological saline added to {100ml }**100 ml.**

{Above }**[0028] The above**-mentioned dextran (produced by Shanghai Glucose Factory), {hydroxyethylstarch} **hydroxyethyl starch** (prepared according to preparative example) are dissolved in physiological saline, and adsorbed and discolored with activated **charcoal** according to the method stated in Example 1. Then **the** above-{ }mentioned sodium chloride, sodium bicarbonate, are added in turn, and dissolved with stirring. {There after} **Thereafter,** the obtained solution is discolored, filtered, sterilized and filled, to obtain the pharmaceutical composition of the present invention.

[0029] Example 3.

Prepare according to the following proportion:

polyvinyl-{ }pyrrolidone (PVP) (produced by Bayer) {12g} **12 g.**

sodium chloride {2g} **2 g.**

sodium acetate {4g }**4 g.**

{10%} **10%** glucose solution added to {100ml

}**100 ml.**

[0030] According to the method described in Example 2, except that dextran and {hydroxyethylstarch} **hydroxyethyl starch** is replaced by PVP, sodium bicarbonate is replaced with sodium acetate, and physiological saline is replaced with glucose solution, the composition of the present invention is obtained.

dextran **9 g.**

[0031] Example 4.

Prepare according to the following proportion:

sodium alginate (produced by Nanning Pharmaceutical Factory, Guangxi)	~~{18g}~~ **18 g.**
sodium chloride	~~{1.5g}~~ **1.5 g.**
water for injection.	added to ~~{100ml~~ **}100 ml.**

[0032] According to the method described in Example ~~{1}~~ **1** to prepare the above-~~{}~~mentioned formulation, thus obtaining the pharmaceutical composition of the present invention.

[0033] Example 5.

Prepare according to the following proportion:

pectin (produced by PLA No. ~~{185}~~ **185** Hospital)	~~{3g}~~ **3 g.**
Pentahydroxyethylstarch (produced by DuPont Company)	~~{4g}~~ **4 g.**
sodium chloride	~~{4g}~~ **4 g.**
mannitol	~~{7g}~~ **7 g.**
2% sodium lactate lution	added to ~~{100ml~~ **}100 ml.**

[0034] According to the method in described in Example ~~{1,}~~ **1,** pectin ~~{Pentahydroethylstarch}~~ **Pentahydroethyl starch** and mannitol are dissolved in sodium lactate solution, then sodium chloride is added and dissolved.

[0035] Example 6.

Prepare according to the following proportion:

condensed glucose (produced by southwest No. 5 Pharmaceutical Factory Chongqing)	~~{7g}~~ **7 g.**
N-2-hydroxy propyl acrylamide	~~{2g}~~ **2 g.**
sodium chloride	~~{4.4g}~~ **4.4 g.**
water for injection	added to ~~{100ml~~ ~~}~~**100 ml.**

[0036] Using the method in Example 1, the pharmaceutical composition of the present invention is prepared according to the above mentioned formula.

[0037] Example 7.

Prepare according to the following proportion:

fructose (produced by Shanghai No. 2 Reagent Factory)	~~{5g}~~ **5 g.**
xylitol (produced by Liaoyang organic Chemical Plant)	~~{4g}~~ **4 g.**
sodium chloride	~~{4.8g}~~ **4.8 g.**
water for injection	added to ~~{100ml~~ ~~}~~**100 ml.**

[0038] Using the method in Example ~~{1}~~ **1**, the pharmaceutical composition of the present invention is prepared according to the above-~~{}~~mentioned formula.

[0039] Example 8.

Prepare according to the following proportion:

glycerin	~~{2g}~~ **2 g.**
lactose (produced by Shanghai No. 2 chemistry Reagent Factory)	~~{5g}~~ **5 g.**
sodium chloride	~~{6g}~~ **6 g.**
water for injection	added to ~~{100ml}~~ **100 ml.**

[0040] Using the method in Example ~~{1}~~ **1**, the pharmaceutical composition of the present invention is prepared according to the above-mentioned formula.

[0041] Test ~~{1}~~ **1**: Animal Experiment

From adult healthy hybrid dogs, regardless of sex, under local anesthesia, isolate femoral artery and femoral vein, then insert catheters respectively.

[0042] The arterial duct is connected to **a** CF-~~{-}~~II model monitor of cardiovascular function [Shanghai approval document number: Hu-~~{-}~~Yao-Qi-~~{-}~~Jian (Zhun)-~~{97 22ll03}~~ **97-221103**] to monitor cardiovascular status. ~~{Bleed these}~~ **The** dogs **are bled** to monitor cardiovascular status. ~~{Bleed these}~~ **The** dogs **are bled** to **an** average arterial pressure (MAP) of 40-~~{-}~~50 mmHg for a period of about ~~{15}~~ **15** min. ~~{Maintain this}~~ **This** blood pressure level **is maintained** for 1 hour, then ~~{infuse}~~ the product prepared in ~~{Example 1}~~ **Example 1 is infused** at the dose of 8 ml/kg.

~~{Monitor the}~~**[0043]** **The** cardiovascular function and urine volume **is monitored** over 4 hours after infusion. In the following tables, the blood pressure and other indexes are expressed as percentage of their basal levels respectively, the unit of urine volume is ml/kg body weight/h.

Table 1

Comparison between the composition of the invention and whole blood in equal volume of recovery of Cardiovascular function in dogs with shock. [unit: % compared with respective basal level]

		after transfusion				
		30 min	1h	2h	3h	4h
Systolic pressure	~~{composition}~~ **Composition** of the invention	75±4	76±4	77±4	78±5	79±5
	equal volume of whole blood	67±5 (p<0.01)	69±6 (p<0.01)	73±4 (p<0.05)	73±4 (p<0.05)	77±7
diastolic pressure	~~{composition}~~ **Composition** of the invention	77±5	79±5	81±4	81±5	81±5
	equal volume of whole blood	69±6 (p<0.01)	73±8 (p<0.05)	76±7 (p<0.05)	76±7 (p<0.05)	82±12
average arterial pressure	~~{composition}~~ **Composition** of the invention	76±4	78±4	79±4	80±5	80±5
	equal volume of whole blood	68±5 (p<0.01)	71±6 (p<0.01)	74±4 (p<0.05)	75±4 (p<0.05)	80±8
cardiac contractivity	~~{composition}~~ **Composition** of the invention	77±5	79±5	81±4	81±4	81±5
	equal volume of whole blood	69±6 (p<0.01)	73±8 (p<0.05)	76±7 (p<0.05)	76±8 (p<0.05)	82±12
cardiac output	~~{composition}~~ **Composition** of the invention	105±13	106±14	103±14	106±12	106±17
	equal volume of whole blood	89±10 (p<0.05)	83±18 (p<0.01)	83±15 (p<0.01)	88±23 (p<0.01)	88±16
end-diastolic volume	~~{composition}~~ **Composition** of the invention	82±4	82±3	83±4	84±3	84±4
	equal volume of whole blood	78±7 (p<0.05)	78±9 (p<0.05)	80±7	82±8	84±8

Table 2

Comparison between composition of the invention and equal volume of whole blood

For urine volume in restoration stage in shocked dogs [unit: ml/kg/h]

	after transfusion			
	1h	2h	3h	4h
Composition of the invention	2.23±1.03	0.94±0.22	0.95±0.29	1.00±0.30
equal volume of whole blood	0.33±0.21	0.27±0.16	0.73±0.41	0.61±0.25
	($p<0.01$)	($p<0.01$)		($p<0.05$)

[0044] The composition of ~~{the}~~ Example ~~{1 of}~~ **1 in accordance with** the invention was administered to 48 patients in Hefei No. ~~{105}~~ **105** Hospital, Anhui province. The total effective rate was ~~{100%.}~~ **100%.** Most patients~~{,}~~ had the blood pressure raised, urine volume increased, and the limbs became warm during transfusion. ~~{Several}~~ **In several** patients whom ~~{the}~~ conventional drugs couldn't ~~{already}~~ reverse, the composition of the Example 1 ~~{of the invention}~~ begin to play its role 5-~~{ 10minutes}~~ **10 minutes** after infusion. The circulatory function of patients ~~{has}~~ recovered basically, ~~{(}~~and there were no obvious clinical complications.

[0045] Test 3. Experiment of acute toxicity

~~{when dogs were}~~ **Dogs** given ~~{at}~~ 2.5 times the dosage for ~~{human,}~~ **humans showed** no adverse effects ~~{have been showed}~~. At 5 times the recommended dosage, salivation and vomiting were seen in the dogs. At ~~{3. 75}~~ **3.75** times the recommended dosage vomiting was seen without salivation in the dogs. All the above administered dogs survived more than 45 days. At ~~{7. 5}~~ **7.5** times the recommended dosage ~~{the}~~ death occurred in the administered dogs~~{.}~~ **and** focal hemorrhage was seen in the lungs as target organs.

[0046] The composition of the present invention could be infused through ~~{vein at}~~ the **veins at a** dose of 8 ml of the composition of the present invention per kg body weight. It could be used directly in treating and saving ~~{the}~~ patients with shock, combined injuries or hematorrhea, etc in order~~{,}~~ to reverse the physio-~~{ }~~pathological status of patients and to obtain time for sequential treatment.

[0047] As compared with the prior art, the pharmaceutical composition of this invention has the following prominent features and improvement:

[0048] 1. Greatly decreased volume of transfusion: In general, the dose for most patients is 500 ml, or less ~~{than 500 ml}~~. Even if the patients suffered

from lethal hematorrhea, to infuse only ~~{1/4}~~ **1/4** to ~~{1/6}~~ **1/6** of volume of lost blood is enough. Thus, it could obviously decrease the incidence rate of tissue edema or overload of **the** heart.

[0049] 2. Rapid curative effect just during 5-~~{10}~~ **10** minutes after infusion, the hemodynamics has been improved significantly.

[0050] 3. Good efficacy. As Test ~~{1}~~ **1** showed, the composition of the invention had better efficacy than that of equal volume of fresh whole blood. Moreover, although the composition of the invention has no oxygen-carrying action, ~~{but}~~ it could improve micro-~~{}~~circulation and general status to decrease oxygen consumption and to increase oxygen transport. Thus, at least 50% of blood transfused could be saved, ~~{it}~~ **which** could mitigate the contradiction with short supply of blood, decrease the complications induced by blood transfusion, and reduce ~~{obviously}~~ the economic burden for ~~{the}~~ patients.

[0051] 4. Maintain once of efficacy for long time. As Test ~~{1}~~ **1** showed, after infusion of the composition of the invention, the improvement of hemodynamics and general condition could be maintained more than 3-~~{}~~4 hours, even if all other infusion and drugs were not administered.

[0052] 5. Unnecessary special condition for storage: The composition could be stored at room temperature, simply used infused intravenously or intraosseously and conveniently transported, without special devices and special vehicles.

[0053] 6. Unnecessary blood typing and cross match tests: It is suitable for ~~{individual}~~ **individuals** with any blood type. Thus ~~{the}~~, valuable time could be gained to rescue the wounded and patients.

[0054] 7. Wider uses: It could widely be used in the treatment of patients with shock of various types, brain trauma, burn, combined injuries, cardiogenic shock induced by myocardial infarction of right ventricle, hypotension induced by hemodialysis, biliary pancreatitis, cardiovascular intoxication induced by

narcotic, hepatic echinococcosis, and patients under operation.

[0055] 8. Change of administration model: The composition of the invention could be infused drop by drop intravenously, instead of pushing so it could be conveniently used with less complications.

[0056] In general, as compared with prior therapy, the composition of the present invention possesses unique benefit and ~~{theoretical}~~ innovation, for treating and saving the wounded and patients~~{, so it is active significance. }~~.

ABSTRACT

The present invention relates to a pharmaceutical composition and the method for the preparation thereof, The composition comprises ~~{1.5}~~ **1.5**~6.9% (w/v) of one or more substances selected from sodium chloride, sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, and the like, and 3~~{18%}~~ **18%** (w/v) of one or more substances selected from hydroxyethylstarch, dextran, carboxymethylstarch, polyvinyl~~{ }~~pyrrolidone, gelatin derivatives, and the like as well as the remainder of conventional injections, as long as sodium chloride is not less than ~~{1.5%}~~ **1.5%** (w/v). The pharmaceutical composition of the present invention is used to treat and save the wounded and patients, as well as to treat shock, its advantages include safe and convenient use, rapid and good curative effect, long time maintenance, extensive uses and the like.